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Award Number: W81XWH-12-1-0138

TITLE: Early Detection of Amyloid Plaque in Alzheimer's Disease Via X-ray Phase CT

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REPORT DATE: June 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
June 2015	Annual	15May2014 - 14May2015

4. TITLE AND SUBTITLE

Early Detection of Amyloid Plaque in Alzheimer's Disease Via X-ray Phase CT

5a. CONTRACT NUMBER
W81XWH-12-1-0138

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Office of Grant and Cont Accting
201 Dowman Drive
Atlanta, GA 30322-1018

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In this project, we proposed to develop the x-ray phase contrast CT imaging method for early detection of amyloid plaque in Alzheimer's disease. As specified in SA#1 and the project timeline, the major tasks of Year 1 and Year 2 are the construction and optimization of a prototype x-ray phase contrast CT system to carry out the tasks specified in SA#2 and #3. The prototype x-ray phase contrast CT has been built in the PI's Lab and is working with full functionality (Fig. 1). In the 1st and 2nd years, we accomplished the tasks specified in SA#1 and SA#2. In the 3rd year, we partially completed the tasks specified in SA#3 – acquisition of x-ray phase contrast CT image of AD brain specimen and its comparison with that acquired by the conventional CT (Fig. 7). However, mainly due to two reasons – (*i*) the fabrication/optimization of x-ray gratings were much more complicated and challenging than we initially anticipated and (*ii*) the acquisition of one set of projection data in the x-ray phase contrast CT takes about 12 hours because of the limited output power of micro-focus x-ray tube – we have not fully completed the tasks specified SA#3 that should be accomplished in Year 3. A one-year no-cost extension of this project has been request and approved. We'll continue to work on these tasks and (see Table II for project timeline in the revised statement of work (SOW)). Thus far, under partial support of this award, four (4) journal papers have been published in *Medical Physics* – one of the leading journals in medical imaging, and eight (8) papers published in leading international conferences.

15. SUBJECT TERMS

Alzheimer disease, Amyloid plaque, X-ray phase contrast, X-ray phase contrast imaging, X-ray phase contrast CT

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
c. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	12	19b. TELEPHONE NUMBER *(include area code)*

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Introduction

A. Overall: As the elderly population increases, dementia caused by Alzheimer's disease (AD) has become a major threat to human health[1-3]. Recently, the x-ray CT based on a new imaging mechanism – refraction – is emerging as a new technology to improve CT's capability in soft tissue differentiation[4-10]. We propose to develop the x-ray phase contrast CT imaging method with an x-ray tube and gratings for direct detecting of amyloid plaques in Alzheimer's brain. It is hypothesized that the disparity in refractive property can generate contrast between the amyloid plaques and surrounding neuronal tissues in AD brain and the contrast is sufficient for imaging with x-ray phase contrast CT. Without the involvement of contrast agent or molecular probes, the so-called BBB (brain blood barrier) can thus be avoided. The project started on 05/15/2012. Here is the annual report of the project's progress in year 3. In order to be objective and complete, some of the important progresses made in year 1 and 2 may be mentioned as well, while this report is focusing on the major progress made in year 3.

B. Specific Aims:

Three Specific Aims specified in the proposal's Statement of Work (SOW), which are repeated below:

SA#1 Develop and optimize an x-ray phase CT to explore the methodology of direct imaging of AP;
Outcome: An x-ray tube- and grating-based phase CT as the foundation for the pursuit of SA #2 and #3.

SA#2 Evaluate the x-ray phase CT's capability of imaging $A\beta_{1-40}$/$A\beta_{1-42}$ peptides/fibrils at the concentrations existing in AD brain;
Outcome: A quantitative understanding of x-ray phase CT's capability in imaging the $A\beta_{1-40}$ and $A\beta_{1-42}$ fibrils.

SA#3 Verify the x-ray phase CT's capability of direct imaging of AP in AD using postmortem brain specimens.
Outcome: Quantitatively evaluated and verified performance of x-ray phase CT for imaging APs in AD.

C. Project Timeline:

Primarily due to two reasons – (*i*) the fabrication/optimization of x-ray gratings were much more complicated and challenging than we initially anticipated and (*ii*) the acquisition of one set of projection data in the x-ray phase contrast CT takes about 12 hours because of the limited output power of micro-focus x-ray tube – we have not fully completed the tasks specified in SA#3 that should be accomplished in Year 3. A one year no-cost extension of this project has been request and approved. For clarity, presented in Table I is the original project timeline, while the revised one is in Table II. The new ending date of this project is 05/14/2016/

Table I. The original project timeline specified in the project's SOW.

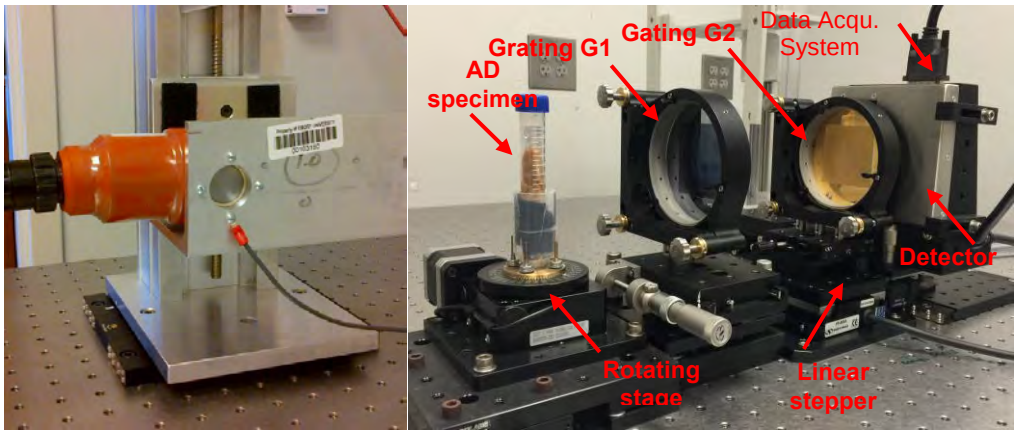
Tasks	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
D.1.1: System construction												
D.1.2: System optimization												
D.2: Performance: Phantom study												
D.3: Performance: Specimen study												

Table II. The revised project timeline specified in the project's SOW with one year extension.

Tasks	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}	Q_{12}	Q_{13}	Q_{14}	Q_{15}	Q_{16}
D.1.1: System construction	→	→	→													
D.1.2: System optimization			→	→	→	→										
D.2: Phantom study						→	→	→	→	→	→	→				
D.3: Specimen study									→	→	→	→	→	→	→	→

Body

According to the revised project timeline, the major tasks in the 3rd year are System Re-optimization and preliminary AD brain specimen Studies. The prototype x-ray phase contrast CT built in the PI's Translational Research in CT lab at Emory Radiology for carrying out this project consists of a micro-focus tube, a CMOS flat panel x-ray detector with 48μm detector cell dimension, a linear motor-driven stepper and the two key components – x-ray gratings G_1 and G_2. The imaging performance of this prototype system has gone through another round of system performance optimization (namely system re-optimization), with an emphasis on improving the performance of G_1 and G_2, and the development of algorithmic solutions to deal with the issue caused by the imperfection in grating fabrication. At the time of this annual report is being prepared, this prototype x-ray phase contrast CT system is fully functioning, with every aspect of imaging performance, but the data acquisition time, approaches our initial design goal (see Fig. 1). It should be pointed out that, the relatively long data acquisition time can be proportionally shortened using a micro-focus tube with a larger output power. Below is a summary of the major progresses made in year 3 via system re-optimization, including the key progresses made in phase de-wrapping, extension of field of view (FOV) in projection domain and image domain, dealing of twin-peaks phenomenon and reduction of artifacts.



(a) **(b**

Figure 1. Pictures of the prototype x-ray phase CT system that is fully functioning in the PI's lab: (***a***) the micro focus x-ray tube and (***b***) the rest of the system, including rotating stage, grating G_1, grating G_2, linear stepper, flat panel x-ray detector and data acquisition system.

A. **System integration and re-optimization – Phase de-wrapping**: Since x-ray grating fabrication is a complicated process, there inevitably exists imperfection in either grating G_1 or G_2, which may cause

phase wrapping phenomenon in the projection data acquired by an x-ray tube and grating-based differential phase contrast CT, as illustrated in Fig. 2 (a), in which the artifacts caused by phase wrapping manifests itself as residual interference pattern (see white arrow heads in Fig. 2 (a)). We developed a phase de-wrapping approach based on a theoretical framework derived by us, which can substantially reduce, if not eliminate, the artifacts caused by the phase wrapping, as displayed in Fig. 2 (b). To the best of our knowledge, this theoretical framework is novel and has been put in to a paper to be submitted very soon to a leading scientific journal in the field.

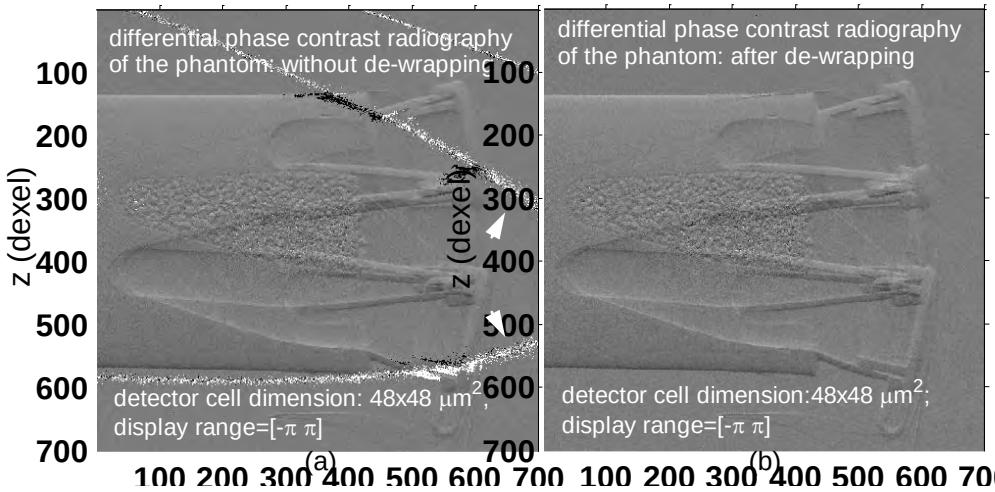


Figure 2. The x-ray phase contrast projection images of the organic material phantom (see its transverse images in Fig. 3) without phase de-wrapping (***a***) and with phase de-wrapping (***b***).

B. **System integration and re-optimization – Extension of FOV**: As we can see from Fig. 2 (b), with phase de-wrapping, the field of view in the projection dmain can be effectively extended to be equal to the active area of gratings G_1 and G_2, i.e., 60×60 mm^2. As such, the FOV in tomographic image can be extended accordingly, as demonstrated in Fig. 3 (b), in which a cylindrical water phantom consisting of four (4) cylindrical targets made of glycerol, alcohol, isopropanol and air (namely organic phantom henceforth) is utilized.

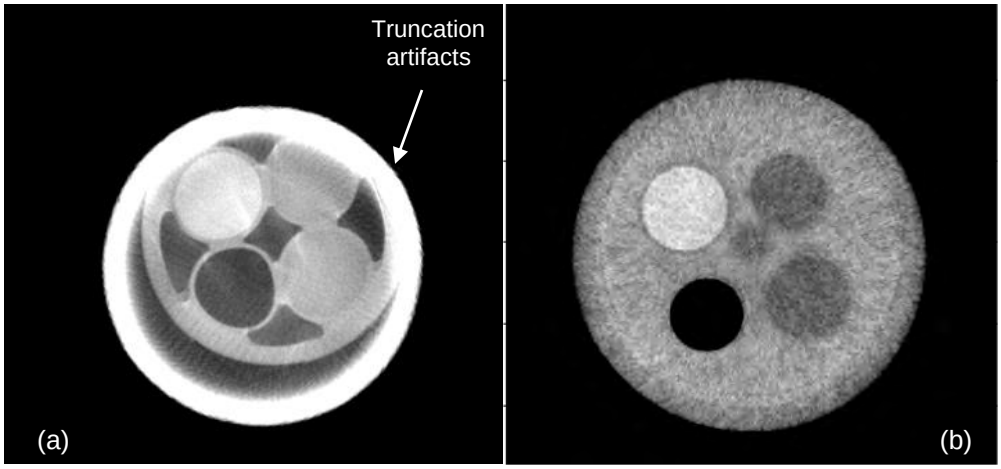


Figure 3. Trans-axial x-ray phase contrast CT images of the organic material phantom with FOV truncated by artifacts due to phase-wrapping (***a***) and with FOV extended by removing the artifacts caused by phase wrapping in the projection domain (***b***).

C. **System integration and re-optimization – Reduction of artifacts caused by twin-peaks in the phase stepping curves (PSCs):** The imperfection in fabrication of grating G_1 and G_2 causes not only phase wrapping in the data acquisition process, but also the so-called feature of the "twin-peaks" in the phase-shifting curves, as illustrated in Fig. 4. If not handled adequately, the twin-peaks can result in artifacts in the reconstructed x-ray phase contrast images, as exemplified by the severe glaring and shading artifacts in Fig. 5 (a). We derived a theoretical framework to characterize the twin-peaks phenomenon in PSCs and developed an algorithm to significantly reduce, if not eliminate, the artifacts caused by the phenomenon of twin peaks in PSCs, as shown in Fig. 5 (b). To the best of our knowledge, this theoretical framework is also novel and has been put in to a paper to be submitted very soon to a leading scientific journal in the field.

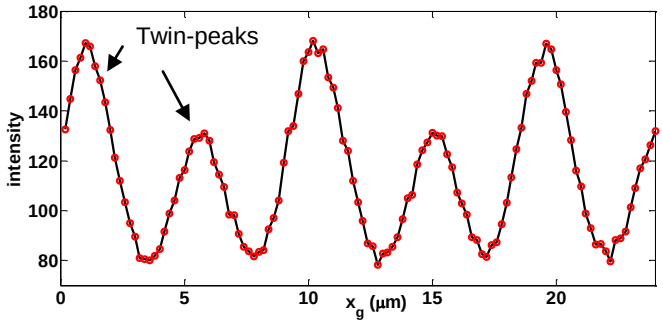


Figure 4. A flat-field (air scan) PSC plotted with data acquired by shifting the absorption grating G_2 120 steps over 24 *μm*.

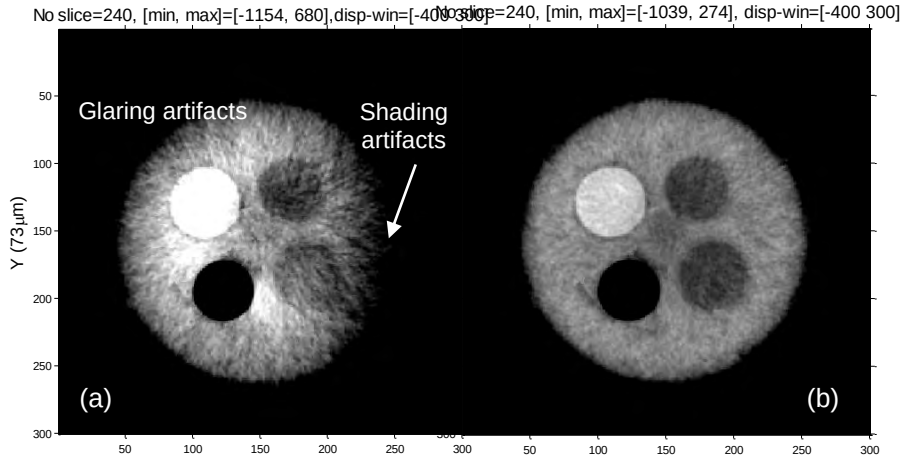


Figure 5. Trans-axial x-ray phase contrast CT images of the organic material phantom corresponding to the cases without twin-peaks handling (***a***) and with twin-peak handling (***b***).

D. **System integration & re-optimization – Imaging performance:** With the re-optimized prototype x-ray phase contrast CT system, transverse phase contrast CT images of the organic material phantom reconstructed from the projection data acquired at cell dimension 96×96 μm^2 and 144×144 μm^2 are presented in Fig. 6 (a′) and (b′), respectively. For comparison, their counterparts in the attenuation contrast acquired at roughly an identical x-ray dose are displayed in Fig. 6 (a) and (b). The contrast-to-

noise ratio (CNR) is measured between the glycerol target and its surroundings. It is observed that, given an identical x-ray dose, the CNR in the phase contrast CT images at detector cell dimension 9×696 μm^2 and 144×144 μm^2 are 140- and 76-fold larger than their counterparts in the attenuation contrast, respectively. This demonstrates that the advantage of x-ray phase contrast CT in CNR over the conventional CT is substantial. Moreover, it should be noted that, because the Hilbert, rather than the ramp, filtering kernel is used in it, the x-ray differential phase contrast CT is much more tolerable to any imperfection that may cause ring artifact in reconstructed transverse images, as demonstrated in Fig. 6.

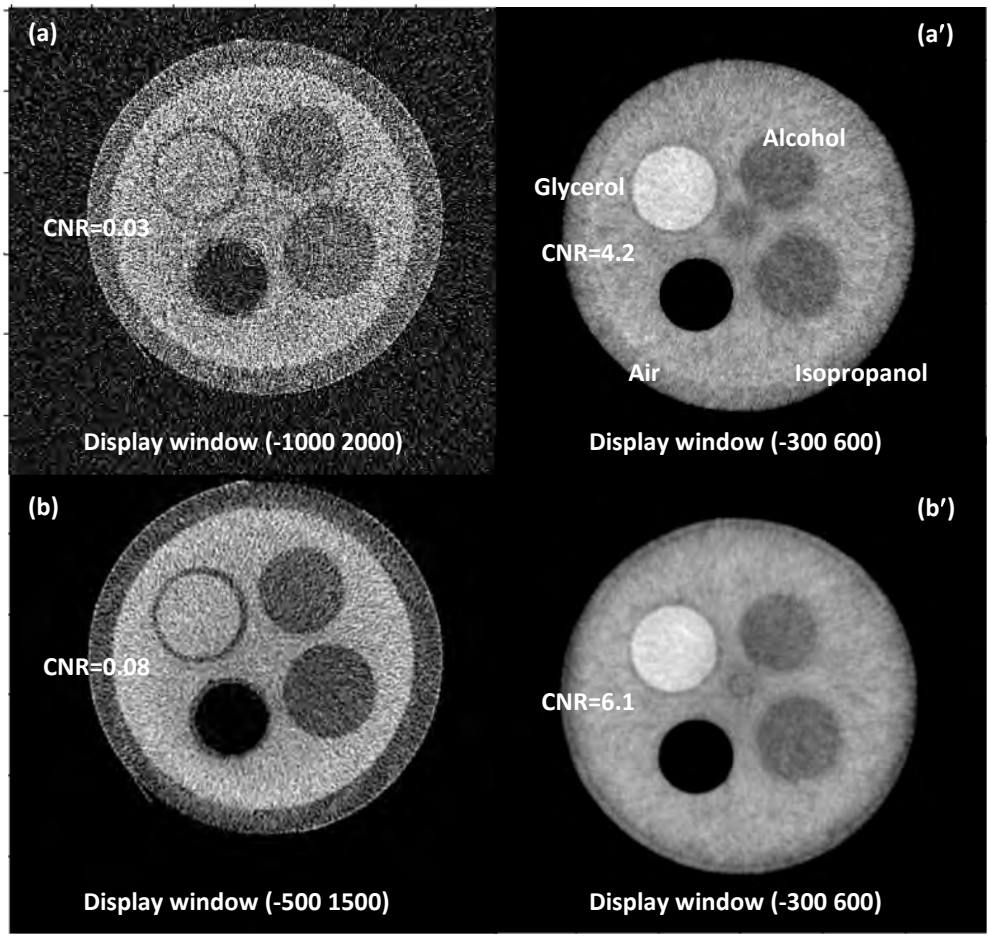


Figure 6. Trans-axial CT images of the organic material phantom corresponding to attenuation contrast (left column) and phase contrast (right column) at detector cell dimension 96×96 μm^2 (top row) and 144×144 μm^2 (bottom row).

E. **Preliminary specimen study**: The installation of the AD brain specimen in the rotational stage is illustrated in Fig. 1 (see the 10 ml lab tube with blue cap). The typical projection images corresponding to the attenuation contrast and phase contrast acquired by the prototype x-ray phase contrast CT system at an angulation are presented in Fig. 7 (a) and (b), respectively. It is observed that, given identical dose, substantially stronger contrast-to-noise ratio are observed, especially at the boundaries of the AD brain specimen (Fig. 7 (b)), in the projection image corresponding to the differential phase contrast, in comparison to that corresponding to the attenuation contrast as presented in Fig. 7 (a). Moreover, the trans-axial CT image corresponding to the phase contrast is shown in Fig. 8 (b), while its counterpart in the attenuation contrast is presented in Fig. 8 (a). In the trans-axial image corresponding to the phase contrast, the gray material and white material are in different CT number, though there is

no clear boundary between them. However, no such difference in their CT number is observed in the trans-axial image corresponding to the attenuation contrast. In addition, there seems some microstructures in the AD brain specimen are observable in the image corresponding to the phase contrast (Fig. 8 (b)), though further investigation by microscopic histology is needed.

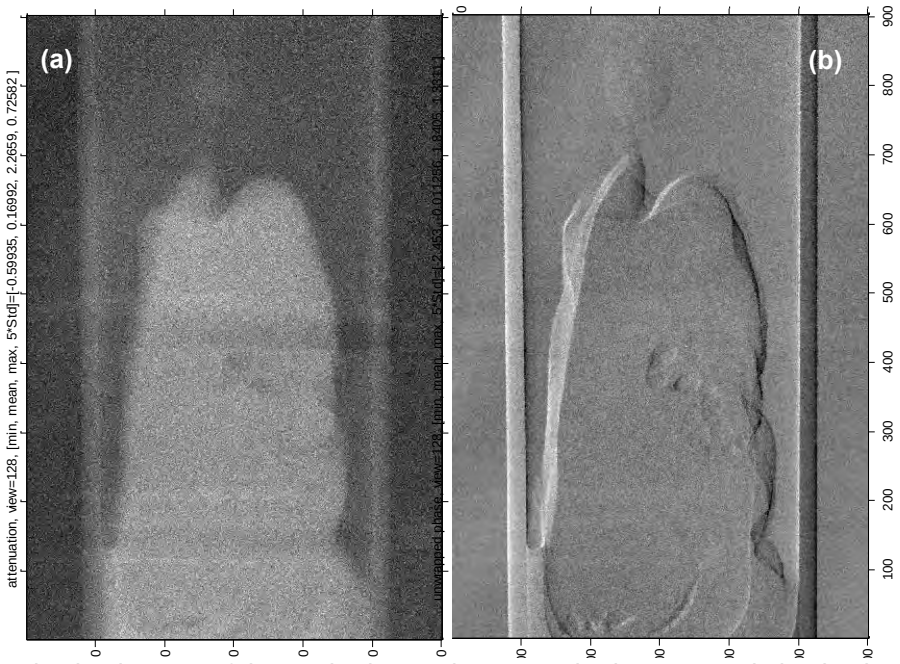


Figure 7. Projection images of the AD brain specimen acquired at an angulation by the prototype x-ray differential phase contrast CT system, corresponding to the attenuation contrast (***a***) and phase contrast (***b***), respectively.

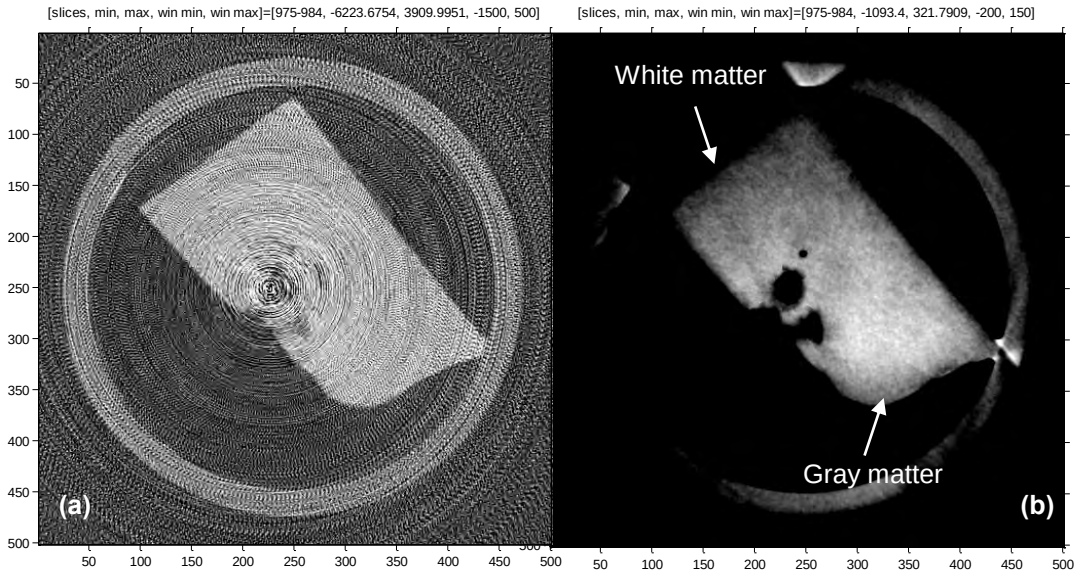


Figure 8. Trans-axial CT images of the AD brain specimen acquired by the prototype x-ray differential phase contrast CT, corresponding to attenuation contrast (a) and phase contrast (b) (in-plane spatial resolution: 48×48 μm; image slice thickness: 0.96 mm).

Major Accomplishments in Year 3

- **System Integration and Performance Re-optimization:** The prototype x-ray phase contrast CT built for this project in the PI's Translational Research in CT at Emory Radiology went through a system re-optimization process and is working at its full functionality with every aspect of imaging performance, except for the data acquisition time due to limited x-ray tube output power, improved substantially, compared to the prototype system's status in year 2. Hence, as demonstrated by the images, both in projection domain and tomographic image domain, the imaging performance of the prototype system indeed has been reached our initial design goals.

- **Preliminary AD brain specimen Study:**
  - Projection images of the AD brain specimen have been acquired and analyzed (Fig. 7). Based on the image quality analysis, the methods to correct for phase wrapping and twin-peak phenomenon have been designed, implemented and evaluated/verified.
  - X-ray phase contrast CT images of AD brain specimen have been successfully acquired with much better contrast-to-noise ratio than its counterpart in attenuation contrast (Fig. 8). More projection data and tomographic image of x-ray phase contrast CT will be acquired and analyzed in the fourth year – the approved one year no-cost extension of this project.

Reportable Outcomes: In Year 3, one paper related to the project was published in Medical Physics, one of the leading scientific journals in medical Imaging, for possible publication. In addition, two (2) papers were published in SPIE Medical Imaging Conference.

A. Publication in Peer-reviewed Journals

1. Yang Y and Tang X, "Complex dark-field contrast and its retrieval in x-ray phase contrast imaging implemented with Talbot interferometry," *Med. Phys., v.40,* 101914 (19pp.), 2014.

B. Publication in Peer-reviewed Conferences

1. X. Tang and Y. Yang, "Internal noise in channelized Hotelling observer (CHO) study of detectability index – differential phase contrast CT vs. conventional CT," *SPIE Proc.* vol. 9033, Medical Imaging 2005: Physics of Medical Imaging, 903326 (March 19, 2014): doi: 10.1117/12.2043251 .
2. Y. Yang and X. Tang, "Complex dark-field contrast in grating-based x-ray phase contrast imaging," *SPIE Proc.* vol. 9421, Medical Imaging 2005: Physics of Medical Imaging, 941257 (March 18, 2015): doi: 10.1117/12.2082294.

Conclusion: At the third year milestone of this project, the following summary and discussions are in order:

- Overall, the project's progression is on track. The fabrication of the two key components – gratings G1 and G2 – has been successful in the 2nd year and re-optimized in the 3rd year, even though it turns out that its success and optimization are yet more challenging than anticipated.
- This prototype x-ray phase contrast CT system is working in the PI's Translational Research I CT Lab at Emory Radiology with full functionality implemented. The imaging performance of the prototype system has been re-optimized through system calibration and imperfection correction, enabling it for future tasks within and beyond the scope of this project.
- The prototype x-ray phase contrast CT system have started carrying out the AD brain specimen studies specified in SA #3, after the tasks specified in SA#1 and SA#2 have been accomplished.

- With the valued support by this award, the research group led by the PI at Emory University has established an international scientific leadership in x-ray phase contrast CT imaging, demonstrated by its publication in the prestigious scientific journals and conferences, and the invitation by journal's editorial board to review manuscripts, and by federal and non-profit funding agencies for the study sections to review research proposals related to x-ray phase contrast CT imaging. Especially, the PI has been the co-chair of a session entitled "Phase-contrast CT and Few View CT" in the 3rd International Conference on CT Image Formation in X-ray Computed Tomography (Salt Lake City, Utah, June 22-25, 2014), as well as the chair of another session entitled "Optical, Ultrasound, and Emerging Imaging Techniques" in the AAPM's (American Association of Physicists in Medicine) 52nd Annual Meeting in Austin, TX (August 20-24, 2014).

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